REMARKS

Before considering the previously raised art rejection, a brief review of the state-of-the art and the problems of the prior art, and the contributions of the present invention would appear to be in order.

Cancer is a major cause of death in humans, particularly in developed and industrialized nations. Various methods for treatment of cancer have been developed, including surgery, chemotherapy, irradiation, and frequently, combinations of two or more of the above.

While surgical and irradiation treatments have been fine-tuned, the most significant improvements in cancer treatment and the greatest opportunity for improvement is in the chemotherapy area. Various anti-cancer drugs have been developed, most of which have serious side effects and disadvantages. These include a high degree of toxicity for healthy cells, increased sensitivity to opportunistic infections, and various types of discomfort for the treated person including, for example, local necrosis of the body structure in which the drug is administered, nausea, vomiting, irritation of the mucoses of the digestive tract, diarrhea, megaloblastose and lesions of the liver or digestive tract, such as stomatitis and buccal and gastro-intestinal ulcers.

Such side effects and disadvantages considerably limit the use of available anti-cancer drugs. Indeed, often a curative effective dose of a cancer drug cannot be given to a patient due to the high toxicity of the drug to normal cells or to the high degree of discomfort caused to the patient by the drug.

The present invention overcomes the aforesaid and other problems of conventional anti-cancer chemotherapy by providing a novel pharmaceutical composition comprising a

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combination of inulin and an anti-metabolic anti-cancer drug, which combination unexpectedly provides a synergistic therapeutic effect on the carcinogenesis and growth of cancer.

Inulins are D-fructans consisting of water-soluble chains of fructose units. Inulin occurs as a polydisperse mixture of linear and/or branched polyfructose molecules as, for example, linear or slightly branched inulin from chicory and from dahlia, and branched inulin from agave.

In view of their almost non-digestibility by alimentary enzymes of humans and non-ruminating mammals, inulins are generally considered to be dietary fibers or non-digestible carbohydrates.

The present invention is based on the discovery that a combination of inulin and an anti-metabolic anti-cancer drug unexpectedly provokes a synergistic therapeutic effect on the carcinogenesis and growth of cancer in humans and in non-ruminating mammals. That is to say, the present invention is based on the unexpected discovery that inulin, a non-digestible carbohydrate, when administered together with an anti-metabolic anti-cancer drug, provides a synergistic anti-cancer effect to a human or non-ruminating mammal undergoing treatment for cancer. As demonstrated in the working examples in the specification, this synergistic effect is unexpected and is unique to a combination of inulin and an anti-metabolic anti-cancer drug, as the effect of combined treatment of inulin and other classes of anti-cancer drugs were found to be only additive (see Tables 1 and 2 on pages 14 and 15 of Applicants' specification).

All of the claims have been rejected under 35 USC §102(b) as being anticipated by EP '252. EP '252 teaches that inulin, oligofructose and their derivatives have properties of value as a functional ingredient in the prevention of carcinogensis or in treatment of cancer.

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EP '252 also mentions, at page 3, that the composition containing inulin may also include "conventional chemotherapeutic products." However, no mention is made in page 3 of a possible synergistic anti-cancer effect of such combination. In Example 7 on page 12, a combination of inulin/oligofructose and an anti-mitotic antibiotic is disclosed. However, no mention is made of a combination of inulin and an anti-metabolic anti-cancer drug as providing a synergistic anti-cancer effect. Applicants submit that EP '252 neither anticipates nor, for that matter, renders obvious any of the pending claims.

As pointed out by MPEP §2131:

> TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM
>
> 'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). > 'When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is [sic] known in the prior art. *Brown v. 3M*, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001) ... .' See also MPEP § 2131.02. < 'The identical invention must be shown in as complete detail as is contained in the ... claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

In rejecting the claims as anticipated by EP '252, the Examiner takes the position:

> The prior art clearly teaches the combination of the claimed oligofructose in combination with an antimetabolite. The synergistic property of such combination is the inherent property of the composition.

Detailed Action, p. 2, ¶2

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In essence, the Examiner acknowledges the synergism of the claimed combination is not taught in the prior art, but the Examiner takes the position that such synergism is an "inherent property" of the disclosed composition.

In contrast to the mechanical arts, the biological arts are considered by the courts to be "unpredictable." That is, a particular result with one system does not necessarily mean one will observe a comparable result with a different, though analogous, system. See, for example, *Genetich, Inc. v. Novo Nordisk*, 108 F.3d 1361, 42 USPQ 1001 (Fed. Cir. 1997).

It is submitted the '252 EP Patent: (1) does not disclose the claimed combination within its four corners, and (2) does not disclose the synergism. Thus, it is submitted, EP '252 fails to teach, or for that matter suggest, exactly what is claimed. EP '252 teaches the use of inulin and/or oligofructose for the manufacture of a medicament that is suitable for the prevention of mammary carcinogenesis and/or the treatment of breast cancer. EP '252 furthermore discloses on page 3, lines 5-6, that said pharmaceutical composition also may comprise "conventional chemotherapeutic products actively destroying malignant tumor cells," as indicated on pages 249-253 of the "Répertoire Commenté des Médicaments," an edition of the Centre Belge d'Information Pharmacotherapeutique (1989). On page 3, lines 8-20 of EP '252 is found a list of the classes of chemotherapeutic products considered as useful, together with examples of specific products for each of said classes.

The disclosure of EP '252 is merely a generic disclosure. Indeed, no specific combination of inulin/oligofructose and an anti-metabolic anti-cancer product is disclosed, and no indication at all is given in EP '252 regarding a possible synergistic effect from the

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appropriate selection, method of selection or basis of selection of inulin and an anti-metabolic anti-cancer drug.

Admittedly, Example 7 of EP '252 (page 10, lines 41-47) mentions that to determine potential synergistic therapeutic effects, a pharmaceutical composition comprising RAFTILINE® (trade name for chicory inulin of ORAFTI, Tienen (Belgium)) and a conventional chemotherapeutic product actively destroying malignant tumor cells, is prepared and a test is described wherein doxorubicine (an anti-cancer drug of the class of anti-mitotic antibiotics) was injected into mice-fed oligofructose/RAFTILINE® and which were previously inoculated with L1210 leukaemic tumor cells. However, EP '252 is completely silent about the outcome of the test and thus about possible synergistic anti-cancer effects between inulin and doxorubicine, and accordingly, in general, between inulin/oligofructose and conventional anti-cancer drugs.

Thus, there is no teaching contained within the four corners of EP '252 of a synergistic anti-cancer effect between inulin/oligofructose and a chemotherapeutic product. Thus, a synergistic anti-cancer effect is neither disclosed nor taught, and hence the teaching of EP '252 regarding compositions that may contain in addition to the inulin/oligofructose a chemotherapeutic product has to be seen merely as teaching compositions seeking the mere addition of the effects of both active ingredients. With respect to the combination of the subject claimed invention of inulin/oligofructose and an anti-metabolitic anti-cancer drug presenting synergistic anti-cancer effects, EP '252 therefore is completely silent and is a non-enabling disclosure.

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Thus, contrary to the position taken by the Examiner, the prior art (EP '252) does not disclose a combination of inulin/oligofructose and "an anti-metabolic drug," but rather at best discloses a combination of inulin/oligofructose and an "anti-mitotic antibiotic," being the only substantiated combination of inulin/oligofructose and a chemotherapeutic product disclosed in EP '252. Based upon the disclosures of the "Répertoire Commenté des Médicaments" (1989), "anti-metabolic" drugs and "anti-mitotic antibiotics" belong to clearly different classes of chemotherapeutic products. Thus, the claims of the subject Application, which specifically read only on a combination of inulin/oligofructose and "an anti-metabolic drug," do not read at all on a composition of the prior art.

Summarizing to this point, EP '252 neither explicitly discloses, teaches nor suggests in an enabling manner a composition according to the present claimed invention containing a combination of inulin and an anti-metabolic anti-cancer drug. Therefore, the subject matter of independent claim 21 cannot be said to be anticipated by EP '252.

It must be remembered the present claimed invention concerns pharmaceutical compositions and their effect on living organisms. Living organisms are notoriously unpredictable, and the effect of pharmaceutical compositions on living organisms also is unpredictable. The claims of the present invention specifically are directed to the combination of inulin and an anti-metabolic anti-cancer drug. Amongst the large group of chemotherapeutic products, anti-metabolic anti-cancer drugs form a particular, well delimited class of compounds. The invention, as claimed, is neither disclosed nor suggested within the four corners of EP '252. That is to say, the particular combination of the inulin and an anti-metabolic anti-cancer drug as claimed in the subject application is endowed with special

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synergistic properties that are not taught by the prior art and could not be expected in view of the prior art, namely, that said particular claimed combination would present synergistic anti-cancer properties. As follows from the comparative tests presented in Tables 1 and 2 of the subject Patent Application, only the claimed particular combinations of inulin/oligofructose and an anti-cancer agent from the class of anti-metabolic anti-cancer drugs present synergistic anti-cancer effects, whereas combinations with inulin/oligofructose with anti-cancer agents from other classes (adriamycin = anti-mitotic antibiotic; endoxam = alkylating agent; oncovin = alcaloidal anti-tumor agent) only present additional anti-cancer effects. Accordingly, the claimed combination of inulin/oligofructose and an anti-metabolic anti-cancer drug presenting synergistic anti-cancer properties can thus be considered as a selection invention. Indeed the properties of a composition containing a combination according to the present invention are clearly unexpected in view of the prior art, even in view of the generic disclosures on page 3, lines 5-20 and page 10, lines 41-47, of EP '252.

Thus, it must be considered unobvious that combining inulin/oligofructose, an essentially non-digestible carbohydrate, with the specific class of anti-metabolic anti-cancer drugs would result in a synergistic effect or potentiation of the anti-cancer effect of an anti-metabolic anti-cancer drug. Thus, not only is Applicants' claimed invention novel, it is unobvious.

Furthermore, on the basis of the prior art, including EP '252, and particularly in view of the uncertainty and unpredictability of the effect of pharmaceutical compositions on living organisms, one skilled in the art could not predict or expect that a particular combination of inulin/oligofructose and a particular class of chemotherapeutic products would present a

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synergistic anti-cancer effect. This is furthermore evidenced by the experimental data presented in Table 1, p. 14 of Applicants' specification, which indicate that a combination of oligofructose/inulin with an anti-mitotic antibiotic or an alkylating agent or an alcaloidal anti-cancer agent merely present additive anti-cancer effects, but no synergistic anti-cancer effects. These data clearly support the claimed criticality to the synergistic anti-cancer effect of the claimed combination of inulin and an anti-metabolic drug.

In the prior Final Rejection, page 2, the Examiner mentions that the specification is not commensurate in scope with the claim language. It is not clear whether the Examiner meant to raise a §112 rejection. However, Applicants state that the experimental data presented in Table 1, p. 14 show that the claimed synergistic anti-cancer effect is not limited to the combination of inulin/oligofructose and a particular anti-metabolic anti-cancer drug (5-fluoro-uracil), but is also provided by the combination of inulin/oligofructose and other anti-metabolic anti-cancer drugs, *in casu* methotrexate.

Applicants have thus proven that the synergistic anti-cancer effect of the combination of inulin/oligofructose and an anti-metabolic anti-cancer drug is not limited to one single anti-metabolic anti-cancer drug. Applicants submit that, having supported the claimed pharmaceutical composition by two examples, their claims to a combination of inulin/oligofructose and a drug from the specific and defined class of anti-metabolic anti-cancer drugs satisfy the requirements of 35 USC §112 and 35 USC §101.

Further in regard to the foregoing, as indicated in the subject Patent Application (specification, p. 16, lines 9-26), the compositions according to the present invention are characterized in that the combination of an anti-metabolite anti-cancer drug and inulin provides

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synergistic anti-cancer effects. In other words, said combination results in the provision of an increased anti-cancer effect compared to the anti-cancer effect of the anti-metabolite anti-cancer drug and the inulin/oligofructose taken alone. This synergistic effect enables to generate to a patient in need of an anti-cancer treatment a higher anti-cancer effect than the effect resulting from a same amount of the anti-cancer drug alone, or to provide to the patient an intended anti-cancer effect by means of a smaller amount of an anti-cancer drug than the amount of said drug that is required without said synergistic combination. The latter case is of high importance when the anti-cancer drug is highly toxic and/or provokes significant undesirable side effects and/or is poorly tolerated by the patient.

As indicated in the specification (p. 2, lines 18-28), anti-cancer drugs are generally classified in seven groups. This classification is based on the chemical class and/or mode of action of the anti-cancer drug. The anti-cancer effects intended by the compositions of the present invention are typically the ones that are provided by anti-metabolite anti-cancer drugs.

Anti-metabolite anti-cancer drugs (also named throughout the specification and prosecution documents as "anti-metabolic anti-cancer" drugs) are substances that are similar to and/or mimic the substances (metabolites) that are needed by cells and cancer cells for normal growth. By the similarity between the anti-metabolites and the metabolites, the cancer cell is tricked into using the anti-metabolite instead. The anti-metabolite anti-cancer drug thus replaces or inhibits the utilization of a metabolite by the cancer cell which then starves because it could not incorporate the proper substance.

The above recites the generally known mode of action of anti-metabolite anti-cancer drugs. From this mode of action it directly follows that the anti-cancer effects of anti-

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metabolite anti-cancer drugs are not limited to one specific kind of cancer. Indeed, anti-metabolite anti-cancer drugs are effective in a more or less pronounced manner against most kinds of cancer because they disturb the normal physiology and growth mechanism of cancer cells, thus resulting in the inhibiting of the growth and proliferation of the cancer cell, and eventually in the dead by starvation of the cancer cell that has incorporated the anti-metabolite.

Accordingly, anti-metabolite anti-cancer drugs are therapeutically used against several kinds of cancer and the kind of cancer against which they are most effective may depend on the chemical structure of the particular anti-metabolite. See, for example, the attached excerpt from the book "Principles of Pharmacology" by P.L. Munson, Ed. Chapman & Hall, 1995, (pp. 1485-1493) reviewing current anti-metabolite anti-cancer drugs and their use. From this document clearly follows that anti-metabolites are effective against a broad spectrum of cancer, including for example: methotrexate against childhood acute lymphoblastic leukaemia (ALL), lymphomas, chorio-carcinoma, lung cancer, breast cancer and diffuse leptomeningeal infiltration with lymphoblastic leukemia (p. 1486, right column, last paragraph; p. 1487, top of left column); mercaptopurine against acute leukaemia in children (p. 1487, right column, last paragraph); thioguanine against various types of leukaemia (p. 1488, left column, last paragraph); 5-fluoro-uracil against many solid tumors, particularly colorectal carcinoma and breast cancer (p. 1492, left column, last paragraph).

In view of the above, Applicants submit that the scope of the present invention fairly extends to the anti-cancer effects generally presented by anti-metabolite anti-cancer drugs, and not to the one exemplified type of cancer. Accordingly, Applicants submit that the scope of the

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invention has been fairly claimed in the currently pending claims and submit that these claims are patentable.

Accordingly, in view of the above comments, the composition of the current main claim (claim 21), which relates to a combination of inulin and an anti-metabolic anti-cancer drug (a specific class of chemotherapeutic products that is clearly different from the class of anti-mitotic antibiotics), has thus to be considered both novel and non-obvious in view of EP '252.

All of the other claims, 22-33 and 35-42, are directly or indirectly dependent on or relate specifically back to claim 21, and also must be considered to be allowable over the art for the same reasons above adduced relative to claim 21, as well as their own additional limitations.

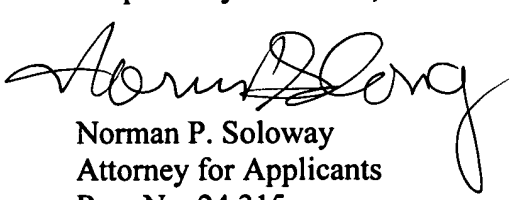
Claim 29 has been amended and split into two claims, amended claim 29 and new claim 41. New claim 42 has been added to further scope the invention.

Having dealt with all the objections raised by the Examiner, the Application is believed to be in order for allowance. Early and favorable action are respectfully requested.

A credit card payment Form PTO-2038 authorizing a charge of $36.00 in payment of the added independent claims accompanies this Amendment.

In the event there are any fee deficiencies or additional fees are payable, please charge them (or credit any overpayment) to our Deposit Account Number 08-1391.

Respectfully submitted,



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